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Fetal Bovine Serum – Geographical Origin and International Trade

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Introduction

It is a common belief that fetal bovine serum (FBS) collected from certain geographical regions, such as New Zealand, is of superior quality to material collected from South America. Whilst it is true that origin does have an impact on the price of serum, it does not affect the quality or biological performance of the product. FBS collected under similar conditions from any geographical region will demonstrate comparable ability to support cell growth. For FBS, the term "quality" is frequently confused with "health status." It is the health status of the geographical region from which the serum is collected that will dictate its potential use, the availability of material for import, and eventually, the price. It should be noted that health status should be considered a result of more than just the geographical source of the material, but also the regulatory infrastructure and how well regulations are enforced by the countries within that region.

The health status of a country is determined by the World Organization for Animal Health (OIE). The mission of the OIE is to ensure transparency in the global animal disease situation. The OIE issues information concerning the health status of various countries with regard to animal diseases of concern, including foot-and-mouth disease, bovine spongiform encephalopathy (BSE), and other diseases affecting cattle populations globally.[1] The status of a country, with regard to the presence of an animal disease of concern, together with interagency government agreements, will determine where serum collected within that country may be exported. Individual countries have varying requirements for importation of serum from the same geographies based on the animal health status of the region from which the serum was collected. **Table 1** provides an overview of the requirements for moving FBS from one part of the world to another. As can be seen, these requirements are extremely complex and are continually changing as regulations evolve. Exporters are strongly encouraged to contact border inspection posts for current requirements prior to shipment of FBS.

For FBS, the suitability of material for certain applications, particularly biopharmaceutical manufacturing, is determined on the basis of the overall

TABLE 1. Example of importation complexity[1].

FETAL BOVINE SERUM (FBS) MARKET ACCESS

IMPORTING COUNTRIES	EXPORTING COUNTRY AND ORIGIN: USA	New Zealand	Australia	Mexico	Central America	Canada	Brazil	Uruguay
Australia	X	X		X				
Bangladesh							X	
Brazil	X							
Canada	X	X	X	X				
Chile							X	
China		X[2]	X[2]					X
Egypt			X					
Europe	X	X	X	X	X		X	X
Hong Kong	X	X	X	X	X		X	
India	X	X	X	X			X	
Indonesia	X	X	X	X			X	
Israel	X	X	X				X	
Japan	X	X	X	X	X	X	X	
Korea	X[3]	X	X			X		X
Malaysia							X	
Mexico	X							
New Zealand	X		X		X	X		
Russia	X						X	
Singapore	X	X	X	X			X	
South Africa							X	
Taiwan	X	X	X	X	X	X[4]		
Thailand							X	
Turkey	X						X	
Ukraine							X	
United Arab Emirates							X	
USA		X	X[4]	X[5]	X[6]	X		
Vietnam	X							

X = Permitted
Information required by importing country typically includes a health certification and documents dependent on port of entry

FOOTNOTES

1. Footnotes 2–5 provide examples of the complexity of importation requirements. Additional requirements exist for other importing countries with respect to certain exporting regions, and this table should not be regarded as complete or necessarily current. Exporters should contact the relevant border inspection post to confirm current importation requirements.
2. Must come from a registered facility and meet importation eligibility requirements for sterility. Must be negative for mycoplasma, bluetongue virus, bovine viral diarrhea virus, bovine leukemia virus, cytopathic effect, and hemadsorption.
3. Requires three-month residency.
4. USDA Safety Testing – bluetongue and Akabane virus (must be negative after testing).
5. USDA Safety Testing – bluetongue virus (must be negative after testing).
6. Excluding Guatemala, El Salvador, and Belize.

health status of the product and the resulting risk to product and patient safety. Serum manufacturers cannot make the determination regarding which geographical region of origin is suitable for the customer's intended use. That is for the end-user to decide. In many instances, end-users (particularly biopharmaceutical and vaccine manufacturers) have committed to specific countries of FBS origin within their regulatory filings. Changing these filings is expensive and burdensome, and requires the customer to re-evaluate adventitious agents present in serum sourced from different regions. It is for this reason that the International Serum Industry Association (ISIA) has developed validated methods by which end-users can confirm that the FBS they have purchased is actually from the region desired.[2]

Risk Mitigation

As discussed earlier, FBS does not differ from country-to-country, in terms of the ability to support cell growth. What differs is the health status of that country, and therefore, the risk of disease transmission associated with the import of the serum. There are steps that can be taken to mitigate some of these risks. These steps include barrier treatments including filtration and gamma irradiation. Filtration through 0.1 micron pore size membranes should remove bacteria and mycoplasmas. Recent publications on gamma irradiation describe a very complex process.[3-8] Even if the irradiation procedures are carried out appropriately, it should be noted that gamma irradiation is not equally effective for inactivating all virus types. In particular, the smallest, non-enveloped viruses such as parvoviruses and circoviruses, as well as certain mid-sized non-enveloped viruses such as polyomaviruses, may survive gamma irradiation at the doses normally applied to FBS.[4] Gamma irradiation may be employed to reduce the viral load in all types of sera, although at higher doses this treatment may also alter the performance of the serum. There is currently no commercial process available to remove prions from serum collected from BSE-affected geographical regions, although blood and blood products are considered low-risk for the transmission of BSE.[9]

Barrier-Free Trade

It is a serum industry goal that serum, collected under supervised and controlled methods and from facilities where animals are slaughtered for human consumption, could share the same status and be shipped globally and without barriers.[10, 11] This is unlikely to happen, however, for a variety of reasons. First, the OIE will continue to monitor animal health and suspend certain geographical regions during outbreaks of animal disease. Second, gamma irradiation at the doses normally applied to FBS will not mitigate the potential risk for transmission of all diseases. Third, international trade agreements for the export of meat from certain areas, and the associated political pressures, will continue to impact the ability of serum to be traded freely. All of these are current barriers for the free movement of FBS.

The ISIA works with regulators globally in order to help them understand the importance of these products and the actual risk, as opposed to the perceived risk, of transmitting disease through blood-derived products. The ISIA is dedicated to education about the truth concerning the safety of animal serum, and works to garner scientific data to further clarify the risks involved. The ISIA will continue to work to develop improvements in the manufacturing and analysis of serum, and to eventually, through the strength of scientific argument, open some of these barriers to allow the harmonized and free movement of FBS in what is becoming an increasingly global economy.

Conclusion

While the possible presence of adventitious agents (including mycoplasma, viruses, and BSE) is an important factor in the selection of a geographical source of origin for FBS, other regulatory and risk management considerations must be understood and acknowledged.

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